Will Modern Therapies Replace Auto and Allo Transplants in Myeloma Treatment?

In just the past 2 months, 3 new drugs for myeloma treatment have been approved by the FDA. In addition to this, there are many more drugs currently undergoing clinical trials. With so many more options for immunotherapy drugs coming up, will transplants (allogeneic and autologous) continue to be an integral part of myeloma treatment? Our myeloma panel comprising of myeloma advocates and survivors, Gary Petersen, Jack Aiello, and Nick Van Dyk will be discussing the subject with Dr. Frits Van Rhee of UAMS, and ex-member and chairman of the Nobel Committee, Prof. Gosta Gahrton of Karolinska Institute. You can follow Prof. Gahrton's presentation here and Dr. Van Rhee's presentation **here**.

Full Transcript:

Priya Menon : Good evening and welcome to CureTalks. I am Priya Menon, Scientific Media Editor of CureTalks, joining you from India. This is CureTalks' 98th episode, and we are talking about significance of transplant in myeloma treatment. My co-host for the talk is myeloma survivor and editor of myelomasurvival.com, Gary Petersen; and supporting Gary on the panel are our myeloma survivors and advocates, Jack Aiello and Nick van Dyk. In the wake of new immunotherapies being approved by the FDA and many more in clinical trials, will transplants continue to be an integral part of myeloma treatment? With therapeutic potential of a myeloma cure, the use of donor stem cell transplantation or allogeneic transplantation is highly debated in the medical field due to associated risks. When does benefit outweigh the risk, and can allo transplants be used to salvage and cure relapsed patients? What about curative potential of autologous transplants? With modern therapies storming the myeloma armamentarium, Dr. Frits van Rhee of UAMS is back on CureTalks discussing auto transplants for treatment of myeloma; and giving his take on allogeneic transplants is Ex-Chairman and Member of Nobel Committee of Karolinska Institute, Prof. Gosta Gahrton. I welcome the experts and the panel to CureTalks. I would like to remind our audience that you can follow Prof. Gahrton and Dr. Van Rhee's presentation slides via the link given on the…, on our website, www.curetalks.com. Before I hand over to Gary, I would also like to remind our audience that we will be addressing questions sent in for the panel towards the end of the discussion. If you have a question for our experts, you can mail it to priya@trialx.com or press 1 on your keypads and let us know so that we will bring you on air to ask your question. With that, its over to Gary. Gary, are you on air? (Pause) I would like to… While Gary is getting…, joining us, I would introduce the experts to our audience. Dr. Frits van Rhee is an internationally known multiple myeloma researcher. He is the Professor of Medicine at the UAMS College of Medicine and Director of Developmental and Translational Medicine in the Myeloma Institute. He joined the Myeloma Institute in 2001, establishing a laboratory for developing innovative medical treatment using the body's immune system. He is a leader of multiple national cancer institute-funded grant projects related to developmental therapeutics and anti-myeloma effects of so-called natural killer cells in the body's immune system. I invite Dr. Frits van Rhee to begin with the presentation. Dr. Van Rhee, you are on air.

Dr. Frits van Rhee : – Thank you very much for inviting me, and its a true pleasure and honor to be on the…, on this show with some of these eminent, as Prof. Gahrton from the…., from the Karolinska Institute in…, in Little Rock. The slides I am showing were recently presented at a meeting in Berlin and just to give the highlights before we take the questions… I think myeloma is always…, has always been considered an incurable disease; and I think that we do have the evidence now that we can actually cure a percentage of

the patients with multiple myeloma with a comprehensive treatment strategy, which we refer to as total therapy. Obviously, if you do want to get long-term remissions and survival, its best to treat patients upfront and early in their disease course rather than when they have had multiple relapses and refractory to therapy. So, any curative therapy needs to be delivered upfront. We have a very good idea about what is myeloma and the mutations that are present in…, in myeloma cells of patients. The problem is that the mutations are rather varied and are present in low numbers of patients and each given mutation and for many of these mutations, we do not have drugs yet and that is probably one of the reasons why what we call total therapy which essentially means all…, applying all available drugs upfront has been so successful, that means combining proteasome inhibitors, immunomodulatory drugs, transplant, and standard combination chemotherapy in a…, in a sequential fashion and the slides will show you that we over the years, we have made progression…., significant progress in individual protocols to such an extent that our…, depending on how you do the mathematics and we have to benefit for very long-term followup, which is unique in our program and we probably can cure in the order of 40% of patients. Now, there is an enormous focus presently on complete remission and minimal residual disease. We can show that the majority of our patients are indeed with long-term followup and in remission are indeed free of minimal residual disease. There is one catch up here. There are certain types of myeloma such as a molecular subgroup, which we refer to as CD-2 molecular subgroup where the…, where the remission rate is quite low, only 25%, and we know historically that these patients do extremely well and have long-term outcome. So, not in all patients we need to eradicate the last myeloma cell in order to have long-term survival. In other words, its not only the presence of MRD which is important but also the quality of cells that remain there. Now, where does immunotherapy come into place? Obviously, allogeneic transplant provides immune effects mediated by the donor cells attacking the…, the myeloma cells and there have been a number of studies and allogeneic transplant is a curative treatment modality for myeloma. I think there is very little doubt about that.

Dr. Frits van Rhee : What are the problems with allogeneic transplant? First of all, the patients can get graft versus host disease which can at times be severe and patients occasionally die and secondly, the…, the immune effect mediated by the donor cells is nonspecific. In other words, its not specifically directed at the myeloma cells and that's…, that's the reason why the donor cells can cause the graft versus host disease. So, there is an enormous progress in…, in immunotherapy; and in fact, 2013 was called breakthrough year for immunotherapy. Those interested in immunotherapy field have for years been trying to induce responses with very little…, with very little success, but we now have a number of treatment options, which are really exciting and allows us to deliver therapies more specifically. So, these are natural killer cells in, which I am interested. There are antibody therapies directed at myeloma cells such as daratumumab and elotuzumab. There are antibodies which release the brake of the immune system and switch on the immune system. They are called checkpoint blockade antibodies, and they are genetically modified T cells. They are very interesting dendritic cell vaccines and they are the normal immunomodulatory drugs and you can actually combine some of these approaches to do a form of what I would refer to as total immunotherapy or combined immunotherapy to get better responses So, we have now the tools to try and induce more specific immune responses directed at myeloma cells without incurring severe toxicity. Obviously, these approaches are first going to be explored in the relapsed refractory setting, but eventually they will move…, move upfront and I would see these therapies as…, as…, as addition initially to current available therapies and in my view, transplant…, the autologous stem cell transplant will still be a very important platform for reducing the myeloma. Its a highly effective treatment modality and…, and can then be followed up by…, by immunotherapy to eliminate the last cells…, last malignant cells that there is, then say couple final things. There is an entity called high-risk myeloma. Now, high-risk myeloma is not uniformly identified amongst myeloma physicians. We used gene array to identify the high-risk disease. So, we looked at the expression of genes in the myeloma cells, what we call high-risk multiple myeloma which is 16% of patients with newly diagnosed disease. We can cure only 20% of these patients and there is a great need for novel treatments started in this group because I think these patients fair poorly in every myeloma center. So, I think the good thing is that myeloma is a curable disease with currently available strategies. Extensive therapy is needed to achieve that, and we hope that with immunotherapy in future we can deliver a less toxic therapy and cure more patients and that we are able to…, to tackle this high risk more effectively. I think I have spoken quite a bit and I think I should give perhaps Professor Gahrton a chance to…, to wade in here.

Priya Menon : We have with us Professor Gahrton who is Professor of Medicine at Department of Medicine, Huddinge, Karolinska Institute, Sweden. He received his MD at the University of Sweden in 1959. Following graduation, Dr. Gahrton joined the famous cell biologist, Torbjörn Caspersson at the Karolinska Institute and late Professor Sidney Farber at Harvard Medical School in Boston. Professor Gahrton has received several honors. Among them the Trafvenfelt Diploma and the A.F. Regnell's Prize from the Swedish Society of Medicine. Dr. Gahrton, we invite you to…, for your presentation now.

Prof. Gosta Gahrton : Okay. Thank you very much. First, I would like to say that Dr. Van Rhee has given excellent overview of…, of the present situation and about the possibilities that are coming. We are… Its a fabulous time with new drugs and new principles of treating multiple myeloma. I think that I should just briefly go through the background in allogeneic transplantation because that is a field I have dealt with mainly. So, if you have my slides in front of you, I will just briefly tell about the study that we made in order to see whether allogeneic transplantation would be better or as good as autologous transplantation and in fact, we didn't look at just allogeneic transplantation. We combined it with autologous transplanation. So, if you had a matched sibling donor, then we would do upfront a tandem autologous allogeneic transplantation and if you didn't have it, we would do an autologous or tandem autologous transplantation. So, that is a study that we made in the European Society for Blood and Marrow Transplantation; and we recruited 357 patients for this study and 108 of these received the tandem auto…., allo transplantation, which with conditioning that these…, the treatment just before the transplant that we call reduced intensity and the reason for that was that we wanted to try to diminish the risks of the transplant, the transplant-related mortality, which is significant with allogeneic transplantation; and the conditioning was not with new drugs because when we started the study around 2000, these were not available. So, we used for induction before the transplant usual cytotoxic drugs and then we conditioned the auto transplant with what is usually done today as well with melphalan and then for the allo transplant that was a program that was actually designed by the Seattle group with fludarabine and total body irradiation with very low dose, only 2 gray and what…, what…, what's important now is that with the tandem auto/RIC allo transplant, the allo transplant, we had a higher complete remission rate and since complete remission is extremely important, we thought this was…, was…., was very encouraging and when we now, 10 years later, analyzed the impact of complete remission, we can see that a sustained complete remission was more important with the tandem auto/RIC allo transplantation. In fact, 21% of the patients were in complete remission at 10 years from the transplant with this procedure, while only 8% were in sustained complete remission with the auto procedure, auto transplant procedure and there is a parallel study by an Italian group that has shown that this might be due to the fact that you have a better quality of the complete remission, a stringent one, with the auto-allo procedure which they have used and in fact, they have an overall survival at more than 10 years of close to 80% if you have a stringent complete remission. So, in that program, the importance of having a complete remission with the auto-allo procedure was very…, very…, it was very important and you could have an important…, a very encouraging survival.

Prof. Gosta Gahrton : Now, there is a problem as Dr. Van Rhee indicated with the allo transplants and that is a problem with graft versus host disease, that is, the graft is…, it attacks the patient in a way. It kills the myeloma cells, but it also has an effect on normal cells. So, the transplant-related mortality in our program at five years amounted to about 50% with this procedure, while in the auto and auto group, it was only 4%, that is also transplant-related mortality with the auto transplants and our thesis counteracted by a lower recurrence rate, a lower relapse rate with the auto/RIC allo and this in turn translate in the better so-called progression-free survival and also of overall survival. In these slides, you can see that in…, in the auto/RIC allo procedure, about 50% were alive at eight years from the transplant, that is half of the patients, which I think is relatively impressive and we also tried to…, to look at the more high-risk group and we didn't have the present important cytogenetic and molecular methods at that time, but at least we…, we could sort out a more high-risk group and also in this one, the survival was the same as in the other patients, about 50% at eight years, while it was significantly low in the auto procedure. So, the conclusion is that progression-free survival and overall survival was better long term, not in short term, but long term with the auto-allo procedure. Now, I must confess that there are other studies that cannot show this. There are two prospective studies that have mainly the same result, that is better for auto-allo, but there are four other studies and one large United States study, the BMT CTN that could not show this advantage and the reason for that is unclear. Now, we have tried to…, to reduce the transplant-related mortality by using new…,

new conditioning regimens. We have in a few, in a small sets of patients used fludarabine and treosulfan and with a relatively short observation time, we could show that this conditioning regimen seemed to be better, in fact, short term, we end up in close to 90% survival despite the fact its not only upfront patients and there are other studies now going on to improve result with allogeneic transplantation using the new drugs, bortezomib and the lenalidomide, in the treatment program and I believe that the new drugs that Dr. Van Rhee was talking about will probably be included in new studies on allogeneic transplantation.

Prof. Gosta Gahrton : I will just show one more…, couple of more slides where you can show that the situation is in Europe concerning allogeneic transplantation. In fact, 600 patients receive an allo transplant every year mainly outside clinical trials which is a pity; and in the next slide, you can see that the main…, the highest number of patients, the green part of the figure, is in fact done in patients that have received more than one or at least one or two auto transplants before they are progressing, while few are received upfront, but the amazing thing is that if you use allo transplant after progression, the results are fair. If you see in the curve, the worst cases with more than two auto transplants before the allo, that is more than two relapses, 24% survival in five years. So, I think that it will be difficult to get rid of even allo transplant totally and definitely not auto transplant. There are two studies recently that have shown that auto transplant even with new drugs in the control arm without the auto transplant is better than if you don't use auto transplant. With allo transplant, there are no good studies using the new drugs yet to be analyzed. so, that I hope will be done and then I think there are some studies now will start in early relapse because early relapse after auto is a poor prognosis and in there it may be possible to use allo transplants, maybe in combination with new drugs. So, there… there I will stop and I will take questions.

Priya Menon : Thank you very much, Prof. Gahrton. We have Gary Petersen with us. Gary, its over to you now to start with the questions.

Gary Petersen : Yes. Thank you so much, Dr. Van Rhee and Dr. Gahrton for…, Gahrton for coming on line with us. Sorry, I was a little late. Its just too much chemo over time, I think. I was a little late in getting on, so I apologize for that, but I would…, would like to say one thing. Dr. Van Rhee has always been so kind whenever I have asked him to review somebody's information and he has always been so, so responsive that I really do appreciate that. I wanted to take this time in order to do that; and Dr. Gahrton, I am just glad that you are able to come on line. Now, one of the things that I have seen, at least I think I have seen, is that with some of the very new drugs like Kyprolis in conjunction with Revlimid and dex and using auto transplant, I think this is done at the University of Chicago and frankly its a, I guess, a multi-center study. When I looked at that data, I noticed that, you know, complete response, MRD and…, and overall response rate were very similar to that which…, and in some cases better than…, than…, than what we saw in TT3. So, you know, I…, I understand its not season, but, you know, how do we know when this becomes the new TT program or will it ultimately not be a durable response? I guess I will open up to…, to both of you.

Prof. Gosta Gahrton : I think that the TT program is probably Frits van Rhee's because they have the…, they have the…, that's their studies, so maybe you…, you answer the question, Frits.

Dr. Frits van Rhee : Now, take the data of the carfilzomib, Revlimid, and dex from Dr. Jakubowiak up in Chicago are very interesting and very encouraging and I think that it attests to the…, to the potency of the carfilzomib with the Kyprolis drug and first of all Dr.Jakubowiak's data do indicate that transplants still need to be part of the treatment. The…, these data showed superior outcome when you actually incorporate the transplants. This is obviously not a randomized study. As you have pointed…, pointed out correctly, there is no long-term followup yet, obviously because its a relatively new approach and incorporation of this type of treatment into a total therapy-type approach is actually very interesting and its very important for us to try and figure it out who actually most benefits from the carfilzomib or Kyprolis drug so that we can give certain subgroups this drug as…, as part of our total therapy regimen. So, its an…, its an important new advance and hopefully will lead to us curing more patients in future.

Gary Petersen : Yeah. The new TT program, right, that includes Kyprolis?

Dr. Frits van Rhee : We have a total therapy 5. We will be working for high-risk disease which includes Kyprolis and we are working on a followup of our…, our so-called low-risk group which is again defined by profiling and we are working on incorporating daratumumab there and…, and other…, other drugs. So, I think total therapy-type approach is a…, is a moving target, its always been, incorporating the novel treatment modalities and the overall aim is to…, to cure more patients and also to reduce toxicity and…, and length and intensity of treatment. I think that has to be an important aim as well. So, I think the data of Dr.Jakubowiak are very interesting, very exciting and I think we are all enthused by it.

Gary Petersen : But…, but, not sure its ready for prime time.

Dr. Frits van Rhee : Oh, I think its a very good treatment approach. I wouldn't say its not ready for…, for prime time, but we would like to still use a more comprehensive approach, which will surely deliver multiple drugs in an induction, transplant, consolidation, and maintenance phase because we know that with that platform we can actually achieve cure. So, we want to build on that and make it better and…, and less toxic.

Gary Petersen : And one of the things that's always, you know, and I want to kind of follow up on that point and I would like to ask Dr. Gahrton a question as well, but the…, you know, the universal, let's say, question with regard to TT is that its never been tested against, you know, like a blind test against another very good approach and it hasn't been multi-centered. As a result, people just don't seem to buy into it. They…, they don't believe it and…, and for me, you know, I happen to have been from a…, you know, been in total therapy at Little Rocks. Obviously 9-1/2 years later and having dialysis-dependent kidney failure, I kind of feel that, you know, its…, its a good approach and I think that other people as well, for example, Pat Killingsworth said once to me, "Boy, I wish I would have had an opportunity at least to know about it," and its not…, it still doesn't seem like its getting better but its not in a…, its mainstream and the only way you can put this thing to bed is to do a head to head, like with TT3 with Kyprolis against the KID plus transplant consolidation and…, and maintenance and once you have done that, that resolves that key question and more…, more people who might…, might take on that program, you know, can't…, can't that be done? I know there is an ethics question. I know that Dr. Tricot has that question, says I am not going to give somebody something that I don't believe is better, you know, is the best approach. Dr. Barlogie says the same thing and that its an ethics issue. To me, its an ethics issue not to do it because so many people don't have that option because they don't believe that that…, that the tests have been done correctly to show its value.

Dr. Frits van Rhee : Now, there are a couple of comments to make there. First of all, if you look at the clinical trial design, some of the European studies, they use a sequential therapy approach and is essentially a total therapy-type approach and we can argue about the drugs, but there is some form of induction, there is a list of transplants. There is often a consolidation and there is certainly a maintenance and then we can all argue about which drugs we should incorporate and whether it needs to be the total therapy cocktails, but certainly the concept of induction-transplant-consolidation-maintenance has been embraced by many centers. It is true that the total therapy approach is aggressive and it requires a comprehensive infrastructure, so it can only be delivered in academic centers. It cannot be done in…, in the community and I would second your remarks about…, from Dr. Tricot and…, and Dr. Barlogie who have been instrumental in pioneering the total therapy approach that when you have something which appears to be working, you don't want to randomize it to something which you think in your heart is inferior. As a doctor, you are probably going to be a little uncomfortable with that.

Gary Petersen : And I say that I understand it, but now with all these…, with…, with, you know, the University of Chicago's information that you can actually put side by side that looks to be equally as good and finally put this multi-center, you know, not invented-here-nonsense to sleep, you know, behind you and…, and more people, more patients can…, can…, can get benefit from it. Now, that's a patient's perspective, you know, that's my perspective, that's Pat Killingsworth's perspective, you know, and we just like to see it done, but…, I'll get off my soap box, I apologize, but I just can't see why it hasn't been done and more people can take advantage of it. Dr. Gahrton!

Prof. Gosta Gahrton : Yeah. May I…, may I just…, may I just comment on these? I…, I think in fact you are

right. I am very much in favor of prospective comparative studies and if you take the study with carfilzomib, lenalidomide, and dexamethasone versus bortezomib, lenalidomide, and dexamethasone, this is a very good study and…, and in fact, it shows very clearly that carfilzomib is probably the best drug if you compare to bortezomib. So…, so…, and that could not have been…, been… You could not have made that claim without these prospective randomized study, just having one of the drugs, the one that you would get exchanged for the one you usually use. So, I…, I think prospective study has a point. I am not criticizing the TTP and…, and several studies in Little Rock, but…, but I think we need also these big comparative studies in order to convince ourselves and the patients that…, that the new is better.

Dr. Frits van Rhee : I…, I would actually also agree with that points. The…, the…, and these talks in the Southwestern Oncology Group in the past about doing some formal total therapy study in…, in other centers and using the comparator arm. So, the question is very relevant, but then you also need to have other centers which are able to take part in…, in such study in randomized patients. Certainly, from our perspective, there will be interest in doing that because there are good normal drugs out there.

Gary Petersen : Oh, I would love to see it and patients want to see it, you know, educated patients want to see it. So, if educated patients want to see it, I am sure that those that are yet learning about their disease really would like to know this and…, and, you know, and I would love for you guys to make it happen, you know.

Prof. Gosta Gahrton : It…, its… I have just commented that it is, of course, a long way to go because first you have this, you know, phase 1 study to see if the new drug is…, is not too toxic and then you have the phase 2 to see that its…, its effect…, it has efficacy, but then I think for a phase 3, that is the prospective one and that's what you ask for and I think you are right, its needed.

Gary Petersen : Okay. So, we've got two centers, one in Sweden and one in…, in…, you know, in Little Rock, Arkansas. We got the beginning here. (Laughter) All right. What if one last question, Dr. Gahrton, and that is with respect to allo transplant. When I go to Be The Match, which is the…, you know, its our historic data for allo transplants, you know, the first year…, first-year survival is usually between…, you know, between 30 and…, you know, the death rate is between 30% and 50% and that would change much. So, are you doing something different than…, than to bring the…, better the…?

Prof. Gosta Gahrton : With the so-called reduced intensity conditioning, its not 30%. Its around 12%. Between 10% and 15% is the initial death rate and its high and its not good and we are trying to find other conditioning regimens that are better, but for the time being, I don't think that upfront allogeneic transplant should be done in the patients that are not high risk, but with very high risk and the very high risk could be with certain chromosomal abnormalities and then, of course, if you have progressed, you have had the first autologous transplant and the drugs and then you have had a remission and then you relapse very soon, that is a poor prognostic sign and I think many agree that we should there start a prospective study with allogeneic transplants and you could even do it outside a clinical trial. That's done in Europe alone. So, there are some subgroups that we should…, we should restart with the allogeneic and not do it in low-risk patients upfront because there I think 15% risk of death is too high.

Gary Petersen : All right. Well, thank you so much, doctor. I would like to go to…, to Jack right now. Jack, are you on line.

Jack Aiello : I am on the line.

Gary Petersen : Jack, your questions?

Jack Aiello : So, I appreciate both doctors writing their presentations. Dr. Van Rhee, I think I heard you say that you are showing 40% cures for standard risk patients and even 20% cure for high-risk patients. Can you define what you mean by cure because I…, doesn't total therapy also involve maintenance to progression and are these patients still on maintenance or do they drop off maintenance? How does that work?

Dr. Frits van Rhee : Our…, our concept of what we call maintenance is actually total therapy, but we call it maintenance but its really extended treatment for three years. So, at the moment we don't keep patients on treatments indefinitely. So, our standard regimen is three years. Obviously, we don't know precisely how long maintenance should be, whether it should be longer or shorter in some patients and perhaps future of minimal residual disease studies and the biology of these persistent cells in certain patient subgroups can help us to guide the duration of the maintenance in…, in future.

Jack Aiello : Okay. Thank you very much and…, and did I…, I did hear you correct that 20% of the high risk patients are showing cure.

Dr. Frits van Rhee : Yeah and these are patients that we…, we define by gene expression profiling. So, there are other ways of defining high risk by cytogenetic methods or by FISH. So, the gene expression profiling definition is very stringently defined group of patients. They are truly very aggressively behaving high risk. At present, if you look at the (4;14) translocation, only about one-third of those patients are actually high risk by our definition. So, there is some confusion in the field what is actually high risk. We have patients coming to us and say, "Oh, my doctor told me I have high-risk myeloma," and then when we use our definition, then patients are low risk. So, its important to…, to…, to bear these nuances in mind.

Jack Aiello : Yeah, I agree. I think even Mayo has (4;14) as intermediate risk. So, these patients that are cured, listening to what you said, means that they are now off treatment and they have probably been off treatment for six or seven years if 10 years is your cure number. Is that correct?

Dr. Frits van Rhee : Yeah. You can see the patients stopped coming out of remission around 9 or 10 years. So, the curve becomes flat and there is a plateau in the curve and you can see that in the slides. So, what is clear though that there's an important lesson to be learned there and that you truly need to follow patients very long term. Our total therapy 1 approach was initiated in 1989. It is 25 years ago. So, one has to be a little careful with drawing conclusion…, conclusions from trials with short followup. We learned in…, in our total therapy 2 trial, which was a randomized trial and one arm had no thalidomide and one arm had thalidomide and it required a followup of eight years to see a difference in overall survival, although there was an earlier difference in progression-free survival. The point is that that in order to appreciate effect of interventions and assess the potential of cure, long-term followup is really quite crucial. We don't at this moment in time have validated, established tests for biomarkers, which can replace long-term followup. So, we don't have the data yet that, say if you have a certain treatment and you are MRD negative at three years, that you are going to be cured of your…, of your myeloma and…, and… So, there is a need for what I would call surrogate tests in order to be able to predict long-term outcome of certain treatments.

Prof. Gosta Gahrton : I can say that I fully agree with Dr. Van Rhee on…, on long term. You have…, you have really have to follow these patients long term if you want to use the word "cure," but there are a few patients cured. The first patient that the Bologna group transplanted in 1986 had survived in complete remission until now, 28 years later. I was told by Dr._____ recently and we have few patients out 25 years, but even after 10 years relapses occur. So…, so, its…, its…, its not a very… Its very difficult with the…, with the cure definition.

Dr. Frits van Rhee : Maybe I can something to that. I mean, we do know that late relapses occur in other…, in other malignancies such as acute leukemia, Hodgkin's disease and nobody argues that these diseases are…, are incurable. So, the fact that there is an occasional late relapse in myeloma doesn't necessarily imply that its an incurable disease. I mean late relapses occur in other malignancies which are well recognized and incurable as well.

Prof. Gosta Gahrton : I agree on that.

Jack Aiello : Dr. Van Rhee, one of your slides titled where to apply curative therapy shows a big arrow at smoldering myeloma patients. Are you suggesting that all smoldering myeloma patients get total therapy?

Dr. Frits van Rhee : No. Obviously, the smoldering patients are really a subset that really comprise of two subgroups. One subgroup more has MGUS-type disease and a second subgroup is early…, early myeloma and you could argue that if we can identify what you call high-risk smoldering multiple myeloma where there is a very high risk of progression to find myeloma that these patients require myeloma therapy and there is a model for risk progression by the Mayo Clinic by Salamanca. We have a gene expression profile and defined model where we can identify patients where the risk progression at a rate of 80% in the first two years. I must argue that these patients require myeloma therapy and obviously there is also a Spanish trial which shows that intervention with Revlimid and dexamethasone in high-risk patients at least unofficially and these are high-risk smoldering multiple myeloma patients, patients with high risk of progression.

Jack Aiello : And Dr. Gahrton, you used the reduced intensity allos followed by an auto only if the patient had a matched sibling. Correct?

Prof. Gosta Gahrton : We…, we always use reduced intensity conditioning if we are going to do an allogeneic transplant today for multiple myeloma. So…, but in the study, we…, in order to make something that…, that is similar to randomization but is not really randomization, you could base your study upon the availability of the sibling donor and only perform transplant with sibling donor and if you don't find a sibling donor, then the patient goes to the control group, that is autologous transplant. So, that's how…, how the sibling donor issue relates to the study.

Jack Aiello : And in practice, since the tandem auto group didn't do as well, are you also using unmatched donors to do allo?

Prof. Gosta Gahrton : Today… In that study, we didn't do that. In the study, we only used siblings, but today…, and today we don't do upfront transplants unless the patient has high risk. So, that means that for patients that have relapsed, that is the target group, first relapse in a relatively shortly after a remission. There we can use those unrelated donors and in fact, today also haploid and so-called haploid anti-donors, that means family donors, parents or siblings that are not fully matched, that are not identical and new data on these type of transplants show that you can get practically the same results with the haploid anti-donor as with a sibling donor, not…, not exactly but close to I would say. So, therefore, in case you do not have a sibling donor and you think there is an indication for allo transplants, you can use either an unrelated donor or a haploid anti-donor.

Jack Aiello : Thank you both very much. I will turn it back over to Gary. (Pause) Gary!

Gary Petersen : Hello! You guys hear me now? Okay. Sorry about that. Dr. Van Rhee, one of the things that I saw on one of your slides is that you have mentioned that people who are over age 65 have a, you know, higher than acceptable transplant-related mortality. I thought, you know, at really the…, at Little Rock, you guys were doing pretty good with people 75 or even greater in your…, in your total therapy program. Am I wrong?

Dr. Frits van Rhee : There are couple of points to make here. This relates… This pertains to treatment-related mortality, not necessarily transplant-related mortality. So, this pertains to mortality of the whole treatment package and we do find that the patients who are over 65, there is more toxicity and mortality and we have modified the approach and give them a lighter version of total therapy. Certainly, transplant as such is not limited by age. Its the biological fitness of the patients which determines whether they can have a transplant or not. Certainly, elderly patients can…, can be eligible for transplant. Deliver very aggressive treatment package such as total therapy in its current form. We presently do not do in Arkansas and we give a modified lighter approach to the 65-year-old or older patients.

Gary Petersen : So, what is the total mortality for TT3 versus that for someone 65 or older?

Dr. Frits van Rhee : Its in…, in…, its in the order of 8% to 9%.

Gary Petersen : For the older ones or overall?

Dr. Frits van Rhee : In the…, in the older patients. So, it varies a little bit between total therapy protocols, but it is clear that there is an increased toxicity signal in the…, in the older patients. So, we…, we are now pursuing a slightly milder approach there.

Gary Petersen : And for just those younger patients, what is it?

Dr. Frits van Rhee : The younger patients, at the moment we are…, we are doing what we call total therapy 4, which is two inductions, two transplants and those are just consolidations and maintenance for three years and we have our new protocol for the low-risk patients in an advanced stage of development.

Gary Petersen : So, what is the mortality for that group?

Dr. Frits van Rhee : Oh, for that…, mortality is low for that group. Its a couple percent, like Dr. Gahrton says.

Gary Petersen : So, its significantly different?

Dr. Frits van Rhee : There is a significant difference there, yes.

Gary Petersen : Okay. We have a number of questions. Priya, would you like to open it up for caller questions and I'll ask the questions that we have got a number that have been written in for us. Priya, any questions from our callers?

Priya Menon : Callers, if you have a question for our panel, you can please press 1 on your keypads and we can bring you on air to ask them. Gary, you can start with the questions…As and when people try to call, I'll let you know.

Gary Petersen : Okay. Yeah. One…, first question is and its probably one that is getting a lot of attraction these days, has to do with immunotherapy and vaccines. Please tell us about the development in the field of multiple myeloma treatment for vaccines. Are there any under clinical trial that we as patients can get access to?

Prof. Gosta Gahrton : That's for you, Frits. I am not so impressed about the vaccine studies. They haven't shown much in my opinion, but you might have other information.

Dr. Frits van Rhee : Well, there is… There is an important….study in America which uses dendritic cell vaccine. Dendritic cells used in myeloma cells are selected by Dr. Avigan and is combining that with Revlimid during the maintenance phase after the stem cell transplant. So, that's going to be a very important study which will establish whether vaccine therapy together with immunomodulatory drug is going to be open for this and…, and can perhaps be incorporated in the future approaches. I think in general…, general terms, there has been a very large number of studies performed with vaccination in multiple myeloma and the results have not been encouraging. So, it appears that a vaccine alone is not sufficient and if you do need to combine it with another immunological approach to enhance efficacy of the vaccine which could be an immunomodulatory drug or perhaps even an antibody which takes the brake off the immune system. There are a number of possibilities there.

Gary Petersen : Also, we have a question with regard to the new monoclonal antibodies. They are supposed to be far more powerful and safe. They are being investigated. How far is the use of bispecific antibody from practical…, practically being used to treat myeloma? Do we have a bispecific antibody trial for myeloma?

Prof. Gosta Gahrton : To my knowledge, not too much, however, in experimental system, they are very

interesting and I think those… The bispecific antibodies and the chimeric antigen receptor T cells, I think, probably is the future because both of them have the kind of specificity for a certain antigen on the myeloma cells and…, and that is, I think, the way to go, but to talk about the results that you can judge for patients, I don't know about those studies ongoing to…, to interpret them. I am not sure I can do that, maybe Frits can do it better.

Dr. Frits van Rhee : No, I think that Prof. Gahrton is absolutely right. They are both very interesting approaches. They…, they are very specific. They will target the immune system to the myeloma cell, but studies are very early…, early in their progress and we'll have to learn how effective these therapies are…, are going to be. They are currently available…, commercially available monoclonal antibodies are actually not bispecific antibodies. They target… They do obviously target the myeloma cells. They belong to a slightly different class of monoclonal antibodies.

Gary Petersen : The next question is similar to the…, what do you see as the future for CAR T therapy in myeloma?

Prof. Gosta Gahrton : Yeah. That…, that was just what I was alluding to the CAR T cells because they are transduced with genes that make them specific to a certain antigen on the myeloma cells and I think there is very little limit to what you can do there and…, and I think…, I think, in my opinion, this is the future. Now, I don't know whether you should use T cells or perhaps another cell that's very important and has been used because it has an anti-myeloma effect, that is the so-called NK cells, the natural killer cells, because you can also make these cells specific with a certain antigen receptor that can target the myeloma cells. So, I think this is the…, these are areas that in the future will be very important and I don't know, maybe they will compete with the transplant procedures and if they are very specific and if the features are very good, I mean they could very well compete with this methodology or be a complement.

Dr. Frits van Rhee : One of the exciting things about the CAR T-cell therapy is obviously that I'd like to term the immunotherapy as agnostic to the risk profile of the myeloma. In other words, in principle, the therapy should kill even very mutate cells and particularly in the high-risk myeloma, where patients quite often have a large number of mutations for which we simply do not have currently drugs available and that's where immunotherapy probably can have an…, and early impact, that is the high-risk myeloma group.

Prof. Gosta Gahrton : I agree on that.

Gary Petersen : Well, obviously, there is a need there in the high-risk group that nobody quite saw that. Okay. Do we need to be in complete remission to do a full allo as part of the first line therapy?

Prof. Gosta Gahrton : No, you don't have to be in complete remission. Its an advantage to be in complete remission when you do it, but its not a pre-requisite to perform an allogeneic transplant. If, for example, you can do it in…, in the…, after the first relapse, you make an attempt to have a remission and you indicate complete remission before the transplant, but its not the pre-requisite. You could do the allogeneic transplant without having obtained a complete remission.

Dr. Frits van Rhee : Prof. Gahrton is…, is quite correct and this pertains actually both to autologous and allogeneic transplant. You do not need to be in remission to have a transplant, that's a common held misconcept. In fact, transplant is a modality of getting patients into remission.

Prof. Gosta Gahrton : Right. I agree on that.

Gary Petersen : All right. This one, I guess, is for Dr. Van Rhee. Has total therapy started cutting back on some of the drug combinations and lightening up on the dosing some in the effort to improve your patient's quality of life. Is this true?

Dr. Frits van Rhee : Yes. We have done so-called total therapy light approach in younger patients and

there is a manuscript being…, is currently under submission. In the lighter approach, early data suggests that the outcome may be slightly worse. So, I would not necessarily think in terms of lightening up the approach by choosing different drugs and hopefully with these drugs we can limit toxicity as well.

Gary Petersen : Okay.

Dr. Frits van Rhee : The point I am trying to make is, we want to maintain the…, the concept of sequential therapy, but we can perhaps improve our…, our drug choices and make the…, the treatments more palatable and more convenient for the patient.

Gary Petersen : Great! Given that myeloma patients with severe renal impairment, I was one of those, are generally excluded from transplant programs. What respite does these new developments in immunotherapy in myeloma promise to offer to such patients?

Dr. Frits van Rhee : I would like to say a quick word about that. Renal impairment or hemodialysis is not a contraindication for autologous stem cell transplant. Prof. Gahrton can speak about this more knowledgeably than I do. It is somewhat more of a problem in allogeneic transplants where quite often we use some drugs with toxicity, renal toxicity, in the prophylaxis of graft versus host disease. In terms of immunotherapy, they…, they obviously…, immunotherapy obviously can be beneficial in all patients group…, all patient groups including those with renal impairment.

Prof. Gosta Gahrton : I agree on this. An autologous transplant you can perform with renal insufficient, but we would not do. We would hesitate. We will not do an allogeneic transplant in a patient with compromised renal function.

Gary Petersen : I am surprised about you two guys because when I was at ASH, it didn't seem that you could get two myeloma specialists to agree on anything and you guys are pretty much in line and step, which is good. You think that, you know, we are kind of coming together over time with, you know, a…, a unified understanding of how to attack this, but, you know, its some of these…, it was surprising to see how…, how different the views still are. Does the survival outcome vary depending on whether the donated cells come from a related or unrelated donor after an allo transplant?

Prof. Gosta Gahrton : Yes, the…, the results are somewhat better with identical sibling donor transplants, but today the difference is between result with haploidentical, as I alluded to before, and matched unrelated donors has been minimized and one reason is, firstly, concerning the matched unrelated ones is that you do better typing. You…, you want more antigen compatibility in order to select that donor and if you have a very good match, then the results are more or less similar to what you can obtain with an identical sibling donor. Then, of course, with the haploidentical, we…., its very new, so we don't know really today if they will be as good, but the approach with the type of conditioning and post transplant, the programs that there is today, the results with sibling or matched unrelated donors.

Gary Petersen : Well, thank you, doctor. Another question… For what kind of myeloma patients do you consider mini transplants or reduced intensity conditioning transplants. How effective are these in your opinion? I think you have already answered that.

Prof. Gosta Gahrton : Well, we would in fact prefer only one such transplant and not do….. There have been quite a few transplants done later on in progression again with an auto-allo procedure, but most of the time they are not very successful. A better approach after an allogeneic transplant where you have progression or relapse is to use donor lymphocytes from the donor and that can induce a new remission and we have patients that have had lasting remissions for up to three years after donor lymphocyte infusions following progression after an allogeneic transplant.

Gary Petersen : Okay. Is there any age limit to…, for a patient who is doing well after relapse on Velcade maintenance to go on to an allo?

Prof. Gosta Gahrton : Oh, yes. We don't do allo. We do allo up to not over 65 to 70 years of age with reduced intensity and even that is relatively high, but in the program we made with sibling donors, we had patients up to 69.

Gary Petersen : Okay and then what…, how do you go about finding a suitable allo donor? What are the international success rates for this procedure?

Prof. Gosta Gahrton : Today, its…, its close to 100%. Its…, its… The registries now have 25 million typed donors. Its increasing every day, so I don't know the exact figure today, but you can usually find one. Now, there is also another possibility. In fact, if you cord blood transplants with cord blood stem cells have been done and that is a little more tricky because you have to do…, use several units from different donors. So, I don't think that's to recommend, but its a possibility, but the other possibility that opens up now is to use the so-called haploidentical because that you can find for most patients that have a parent and have some siblings because there you don't need these so called identical type and so that does open up for more donors…, available donors.

Gary Petersen : Okay. That's all the questions we have from, you know, from our listeners. Jack, do you have any other question you want to ask?

Jack Aiello : No, I am…, I am good and I appreciate the doctors spending more than an hour on the phone with us.

Gary Petersen : Yes. Thank you so much, doctors. We really do appreciate it. Priya!

Prof. Gosta Gahrton : It was a pleasure.

Priya Menon : Thank you, Gary. Dr. Van Rhee and Prof. Gahrton, thank you very much. I think it was…, it was great listening and learning too. I think we have gone over our time. Thank you so much for the extra time too. We have come to the end of today's show. Gary and Jack, thank you so very much for your participation. Today's talk will be made available on CureTalks' website along with its transcript and this has been a wonderful year and this is actually CureTalks' last show for 2015. We thank all our audience, experts, and our panelists who stood by us this entire year. Please visit curetalks.com for details of our talks in the coming new year. Wish all of you happy holidays and we will meet again in 2016. Thank you.